Response Under 37 CFR 1.116
Expedited Procedure
Examining Group 1642

A049 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Jurg Tschopp

Application No. : 09/520,489 Confirmation No.: 1565

Filed : March 8 2000

For : APRIL - A NOVEL PROTEIN WITH GROWTH EFFECTS

Group : 1642

Examiner : Karen Canella

#11
6D
7-12-02

New York, New York
June 10, 2002

Hon. Commissioner
for Patents
Washington, D.C. 20231

DECLARATION OF PAUL D. RENNERT, M.S.
UNDER 37 C.F.R. § 1.132

I, PAUL D. RENNERT, hereby declare that:

1. I currently hold the position of Research Scientist II at Biogen, Inc., and I have a Master of Science degree in Zoology from the University of Vermont. My Curriculum Vitae is attached hereto at Tab A.

2. I am familiar with the above-identified application ("the application"), as well as with the July 5, 2001 and January 15, 2002 Office Actions in the application. I understand that claims 36, 37, and 39-49, relating to methods for

suppressing the growth of tumor cells, methods for treating cancer, and methods for identifying agents capable of suppressing the growth of cell cultures, stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, I understand that, in the Examiner's view, the claims are not supported by a description in the specification that enables one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that "the specification did not teach a specific antibody to APRIL...that could prevent the binding of free APRIL to its receptor in a manner which would inhibit the growth of a malignant cell." The Examiner further stated that one "cannot extrapolate results from such experimental systems to solid tumors *in situ*..." because of issues related to biological stability, half-life, clearance from the blood, and target tissue penetration. The Examiner has concluded that "the specification does not provide a nexus between APRIL receptor antagonists and the treatment of cancer *in vivo*."

3. I make this declaration to demonstrate that one of ordinary skill in the art, following the teachings of the application, would be able to make antibodies directed to APRIL ligand polypeptides that are capable of interfering with the interaction between APRIL ligand and its receptor. A person of skill in the art, following the teachings of the application,

would then be able to use the antibodies to treat, suppress, or alter the progression of tumors *in vivo*.

4. The application relates, in part, to antibodies directed to APRIL ligand polypeptides, and their use, for example, in treating cancers, tumors, hyperplasias, or manipulation of the immune system to treat immunologic diseases. The application teaches the nucleotide and amino acid sequence of APRIL ligand polypeptides, including the sequences that comprise soluble forms. The application also teaches methods for producing APRIL ligand polypeptides and using them to generate antibodies directed to the APRIL ligand polypeptides.

5. A person of skill in the art, having recombinant APRIL ligand polypeptides in hand, has the tools necessary to make antibodies directed to APRIL ligand polypeptides because methods for making antibodies were well known in the art by the time of the application's earliest filing date. *See, e.g.*, *Antibodies: A Laboratory Manual*, Harlow and Lane, Cold Spring Harbor Press: 1988. A person of skill in the art, after making anti-APRIL ligand polypeptide antibodies, would then be able to screen different antibody preparations for those that interfere with the interaction between an APRIL ligand polypeptide and its receptor. Therefore, the application, in light of the state of the art at the time of the earliest filing date, teaches a person

of skill in the art how to make antibodies that interfere with the interaction between APRIL ligand and its receptor.

6. As evidence of this, I declare that efforts in my laboratory that followed the teachings of the application resulted in the generation of anti-APRIL ligand antibodies that block the interaction between APRIL ligand and its receptor. Specifically, mice were injected with human APRIL ligand proteins, hybridomas were generated from seropositive animals, cloned, and screened for anti-APRIL ligand antibodies. These screens resulted in the identification hybridomas that generate mouse anti-human APRIL ligand monoclonal antibodies. As can be seen in Figure 1 at Tab B, the C13.A5.3 anti-human APRIL ligand antibody ("the C13 antibody") efficiently blocked the interaction between an APRIL ligand protein and the APRIL receptors BCMA and TACI *in vitro* using an ELISA assay. Similarly, the A13.B11 anti-human APRIL ligand antibody ("the A13 antibody") efficiently blocked the interaction between an APRIL ligand protein and the APRIL receptors (Figure 1). The specificity of this antibody activity was confirmed with the BAFF protein, which has been previously shown to bind BCMA. Rolink and Melchers, Curr. Opin. Immunol. 14(2):266-75 (2002). Figure 2, Tab C, shows that the C13 and A13 antibodies blocked the binding of APRIL protein to the BCMA receptor, but did not block binding of BAFF to BCMA.

7. The application teaches in Example 2 that APRIL ligand drives increased cellular proliferation *in vitro* and *in vivo*. NIH-3T3 cells were stably transfected and several APRIL ligand-expressing clones were established. The APRIL ligand-transfected clones showed enhanced proliferation rates in comparison to mock-transfectants. When mice were injected with the APRIL ligand-transfected clones, tumor burden was dramatically increased over mice injected with wild-type or mock-transfected NIH-3T3 cell lines.

8. I believe that the specification provides a nexus between anti-APRIL ligand antibodies and the treatment of cancer *in vivo*. The combination of (1) *in vitro* studies of cellular proliferation, (2) *in vivo* studies showing an APRIL ligand-driven increase in tumor burden, and (3) the ability to make an antibody directed to an APRIL ligand polypeptide capable of interfering with the interaction between an APRIL ligand and its receptor would lead a person of skill in the art to believe that tumor cell proliferation and tumor burden *in vivo* may be reduced by providing an antibody that interferes with the interaction between APRIL and its receptor.

9. Following the teachings of the application, I have supervised and performed experiments that show that the anti-APRIL ligand antibodies that we generated (*see* ¶ 6, above) reduce tumor burden in mice injected with tumor cells. HT29 colon

adenocarcinoma cells were injected into Balb/c nude mice and treated twice per week with intraperitoneal injections of 100 µg of mouse anti-human APRIL ligand antibodies. As shown in Figure 3 (Tab D), the tumor volume in mice treated with the C13 antibodies was significantly reduced by day 24 post injection when compared to the tumor volume of mice injected with the tumor cells and treated with PBS or MOPC21 control antibodies (MOPC21 recognizes keyhole limpet hemocyanin).

10. Taken together, the application, in light of the state of the art at the time of the earliest filing of the application, teaches a person of skill in the art how to make antibodies that interfere with the interaction between APRIL and its receptor. Furthermore, the application provides a basis for a person of skill in the art to treat tumors *in vivo* with those antibodies to reduce tumor burden.

11. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that such willful false statements may

jeopardize the validity of this application and any patent issuing thereon.

Date: 10 JUNE 2002

Paul D. Rennert, M.S.

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: COMMISSIONER FOR PATENTS P.O. Box 2327 ARLINGTON, VA 22202 on

JUNE 13, 2002

Lillian Garcia

Signature of Person Signing

Paul David Rennert

Biogen
14 Cambridge Center
Cambridge, MA 02142
617-679-2986
617-679-2304 (fax)
Paul_Rennert@Biogen.com

BIOGEN Inc, Cambridge, MA (1995-present)
Research Scientist II, The Department of Immunology

The TNF Family, costimulation, and chemokines:

- The TNF and TNF-receptor families of proteins provide critical signals for the development, organization, and function of the immune system. Our recent work has focused on the complex pathways which control lymph node genesis, and the subsequent steps required to form organized lymphoid tissue. We demonstrated that the lymphotoxin (LT) alpha/beta complex delivers a critical signal for lymph node formation through it's receptor, LTβ-R. Further, both the LT and TNF systems are required for cellular organization within the developing lymph node and spleen. Understanding the role of LTβ-R in these biologies is critical to the success of LTβ-R-Ig fusion protein, currently in Biogen's clinical pipeline. Our work has been published in top tier journals and stimulated collaborations world-wide aimed at unraveling the LTβ-R signaling pathways and the roles that LTβ-R plays in diverse immunological settings.

- The new TNF ligand, APRIL, is a potent inducer of tumor cell growth both in vitro and in vivo. Treatment of immunosuppressed mice with a soluble APRIL antagonist dramatically slows the growth of solid tumors. Our current efforts are directed toward understanding APRIL's mechanism of action on tumors cells, in identifying the relevant receptor which mediates APRIL tumor biology, and in constructing animal models to allow us to develop an understanding of APRIL's normal physiological role, including the induction of proinflammatory chemokines in diseased tissue.

- Other projects my lab is pursuing include characterization of novel Ig-superfamily members with T cell costimulation or Th-development activity, including the B7 and TIM families of proteins. We also provide cellular immunological and animal modeling support for a program directed toward developing an anti-MCP-1 mAb

REPLIGEN Inc., Cambridge, MA (1987-1995)
Associate Scientist, Departments of Molecular Biology and Molecular Immunology

Costimulation and retroviral biology:

- Costimulation of T cells is a complex process which involves multiple ligand/receptor interactions. One well known pathway of T activation is triggered by binding of the CD28 molecule. Structure/function

analysis of the ligands for CD28 produced B7 proteins with novel properties. Expression cloning of activation and apoptotic antigens led to the identification of other critical molecules which control T cell fate.

- HIV and SIV viruses produce an array of structural and regulatory proteins which together mediate the viral life cycle. Exhaustive analysis of the envelope proteins of these viruses revealed that the structural motifs used to engage target cells were dramatically different. The RNA target of the HIV-1 REV protein was identified, which led to the discovery of specific REV antagonists.

HOWARD HUGHES MEDICAL INSTITUTE, Massachusetts General Hospital, Boston, MA (1986) Research Associate, Dept of Molecular Endocrinology

- Analysis of NGF expression in mouse brain resulted in the first description of its localized expression in cholinergic innervated regions of the hippocampus.

UNIVERSITY OF VERMONT, Burlington, VT (1982-1986) Research Assistant and Graduate Teaching Fellow, Dept of Zoology (Dr C.W. Kilpatrick)

- The study of mammalian molecular evolutionary biology led to the identification of two new species of *Peromyscine* rodents in Mexico

- MS., Zoology, 1986

COLBY COLLEGE, Waterville, ME

- BA, Biology, 1980
- BA, Philosophy, 1980

PUBLICATIONS

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5. Sullivan, J.M., C.W. Kilpatrick, and P.D. Rennert. 1991. Biochemical Systematics of the *Peromyscus boylii* Species Group. **J. Mamm.** 72(4): 669-680.

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Luciana Trabach and Paul D. Rennert. 2002. APRIL and BAFF: Similar proteins with distinct activities. Ms. in preparation, review to be published in **Current Trends in Immunology.**

Rennert, P.D. and T. Waldschmidt. Distinct Roles of LTα and TNF in the Maintenence and Function of the Splenic Marginal Zone. FASEB 2001 abstract. Ms in preparation.

Masafumi Yamamoto, Paul D. Rennert, Mi-Na Kweon, Jerry R. McGhee, Shigeo Otake and Hiroshi Kiyono Blockade of both TNF/LTα and LTα/β, but not TNF/LTα or LTα/β, Pathways Results in the Inhibition of Mucosal and Systemic IgA Responses. ICI 2001 abstract. Ms in preparation.

Luciana Trabach, Graham Farrington, Kalpit Vora, John Eldredge, Irene Sizing, Jeffrey Browning, and Paul D. Rennert. APRIL, a Novel Member of the TNF Family, is a Potent Mediator of Cellular Proliferation and Survival. FASEB/AAI 2002 abstract, Ms in preparation.

Laura Runkel, Martin Scott, Paul D. Rennert, and Jeffrey S. Browning. Genetic deletion of APRIL, a new member of the TNF family, causes embryonic lethality due to abnormal heart development. submitted.

PUBLISHED PATENTS (FILINGS WITHIN 18 MONTHS ARE NOT SHOWN)

METHODS FOR SELECTIVELY STIMULATING T CELLS (US5858358, EP00764203A1)

LIGANDS FOR THE INDUCTION OF ANTIGEN SPECIFIC APOPTOSIS IN T CELLS (EP764171A1)

ANTIBODIES AND IMMUNOGLOBULIN FUSION PROTEINS HAVING MODIFIED EFFECTOR FUNCTIONS, AND USES THEREFORE (EP877812A1)

FUNCTION AND USES OF THE V DOMAIN OF B7-2 (CIP, US5942607)

SOLUBLE LYMPHOTOXIN-BETA RECEPTORS, ANTI-LYMPHOTOXIN RECEPTOR ANTIBODIES, AND ANTI-LYMPHOTOXIN LIGAND ANTIBODIES AS THERAPEUTIC AGENTS FOR THE TREATMENT OF IMMUNOLOGICAL DISEASES (US5925351)

ANTAGONISTS OF TWEAK AND OF TWEAK RECEPTOR AND THEIR USE TO TREAT IMMUNOLOGICAL
DISORDERS

APRIL RECEPTOR (BCMA) AND USES THEREOF

A HETEROLOGOUS POLYPEPTIDE OF THE TNF SUPERFAMILY

OTHER PROFESSIONAL ACTIVITIES AND ASSOCIATIONS, Y2000-2002

- ad hoc reviewer, *Journal of Immunology, Infection and Immunity, Immunological Letters, Journal of Pathology, J. Neuroimmunology, Current Molecular Medicine*

- member, American Association of Immunologists.

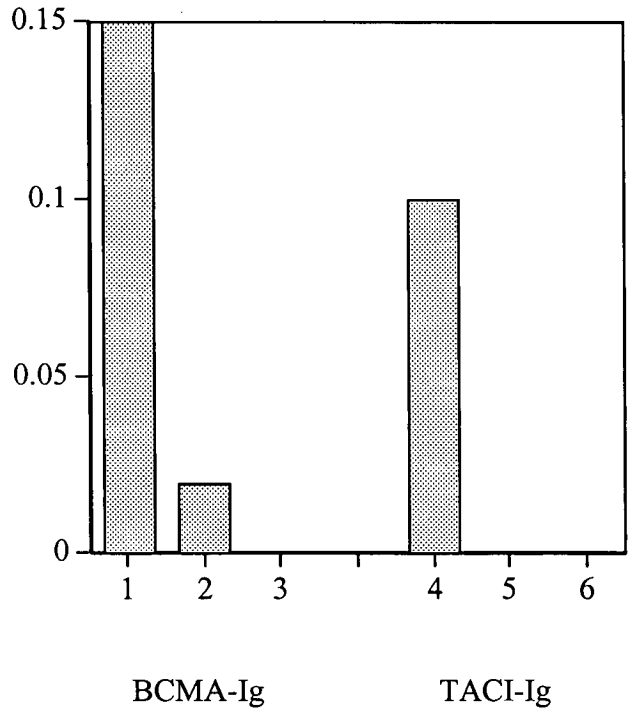
- doctoral thesis committee member, March 2000, MIT (D. Baltimore and R.O. Hynes, co-chairs).

- Member, Scientific Committee, workshop on lymph node development, HHMI

- Cochair, Biogen's Research/IS Desktop and Instrumentation committee, which manages the process of identifying, testing, and deploying desktop, instrumentation, and peripheral solutions for specific needs within Research.

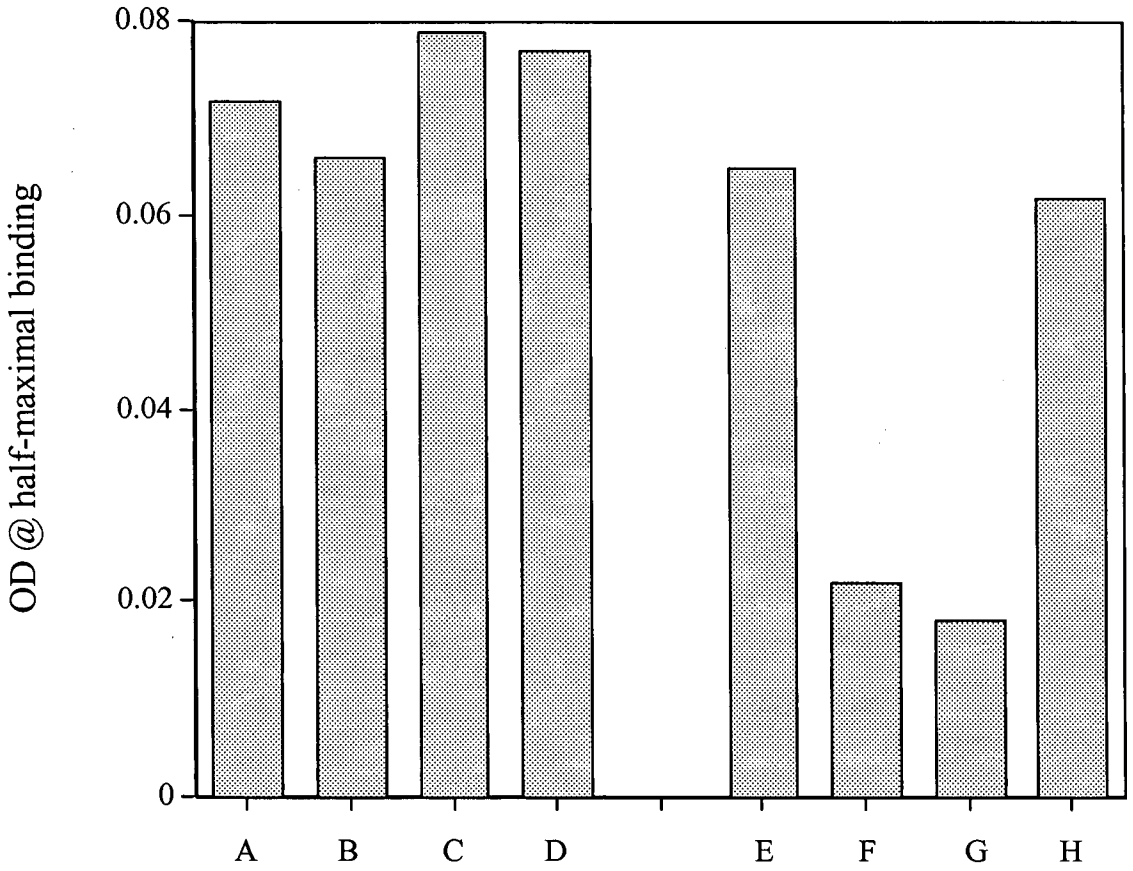
- Member, Biogen's Inflammation Focus Area Team, responsible for assessing in house and external opportunities for programs in immunology and inflammation.

ELISA assay shows anti-human APRIL mAbs C13 and A13 block binding of APRIL ligand to the APRIL receptors BCMA and TACI



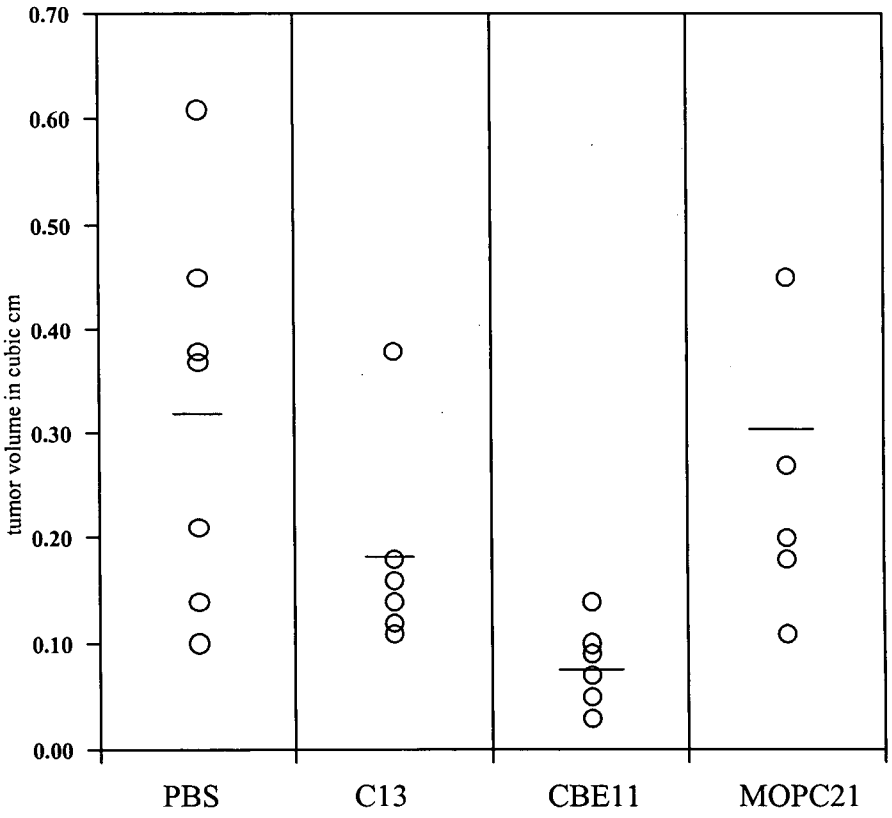
Binding of 150 ng/ml solution of hAPRIL protein to BCMA-Ig (1-3) or TACI-Ig (4-6) coated plates. Columns 1 and 4 show binding in the absence of competition, compared to binding in the presence of mouse anti human APRIL mAbs C13.A5.3 (2 and 5) and A13.B11 (3 and 6).

ELISA assay shows C13 and A13 mAbs specifically block APRIL ligand but not BAFF binding to BCMA



The mouse anti-human APRIL mAbs C13.A5.3 and A13.B11 block the binding of human APRIL to BCMA-Ig-coated plates (F and G, respectively), but have no effect on human BAFF binding (B and C, respectively). The control mIgG1,k mAb does not impact the interaction with BCMA of either BAFF (D) or APRIL (H), as compared to untreated controls (A and E).

HT29 tumor growth 24 days after implantation into Balb/c nude mice



HT29 adenocarcinoma cells were injected into Balb/c nude mice and tumor volume was measured 24 days post injection. The anti-APRIL antibody C13 significantly reduced tumor burden as compared to mice treated with PBS and MOPC21 (anti-KLH antibody) controls. CBE11 is a mouse anti-human LTβ-R which has been previously shown to reduce tumor burden.